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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,073	11/14/2001	Avi J. Ashkenazi	P2730P1C15	4049
35489	7590	02/23/2005	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP 275 MIDDLEFIELD ROAD MENLO PARK, CO 94025-3506			SPECTOR, LORRAINE	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/991,073

Applicant(s)

ASHKENAZI ET AL.

Examiner

Lorraine Spector, Ph.D.

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 122-126 and 129-131 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 122-126 and 129-131 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 11/4/04.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

Claims 122-126 and 129-131 are pending and under consideration.

This Office Action is in response to applicant's amendment filed 11/4/2004.

The new title of the invention is acknowledged.

The rejection of claims 119-131 under 35 U.S.C. §112, second paragraph is withdrawn in view of applicant's amendments.

The rejection of claims 119-131 under 35 U.S.C. §112, first paragraph (deposit requirement) has been overcome by the amendment filed 11/4/2004.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 122-126 and 129-131 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility for reasons cited in the previous Office Action mailed 6/3/2004, at pages 3-5. Applicant argument, filed 11/4/2004 has been fully considered, but is not deemed persuasive, for reasons below:

It is noted that applicants have amended the claims to recite that the nucleic acid encoding the claimed polypeptide is "amplified in lung tumors". The recitation of such raises issues under 35 U.S.C. §112, first paragraph regarding written description (see below), and fails to provide utility, because (a) no significant association between the claimed nucleic acids and lung cancer, such as would lend diagnostic utility, has been disclosed or established, and (b) even if such *had* been established, it would not be predictable that the claimed protein would be similarly diagnostic, as set forth in the previous Office Action.

At pages 8-9 of the response, applicants review the standards for utility under 35 U.S.C. §101. Applicants argue that the Examiner has failed to assert a *prima facie* case of lack of utility is not persuasive; see pages 3-5 of the previous office action. The Examiner maintains that a *prima facie* case of lack of enablement has been established in the previous Office Action. While absolute predictability is not a requirement for utility, the Examiner has established that the skilled artisan would not consider the meager amount of amplification of the nucleic acid encoding the claimed polypeptides in a minor fraction of assayed tissues to be predictive of over expression of the claimed polypeptide in a manner that would allow diagnostic use of such.

Bridging pages 8-9, applicants argue that the amplification of the nucleic acid encoding the claimed polypeptide is significant, and cite a declaration by Dr. Goddard. This argument has been fully considered but is not deemed persuasive because the 2-3 fold amplification of the nucleic acid is not predictive of protein levels.

The declaration under 37 C.F.R. §1.132 by Dr. Goddard has been fully considered. The Goddard declaration is not pertinent, as it is drawn to the significance of the amplification of the nucleic acids, and fails to address the issue of the claimed protein.

At page 10, applicants argue that both the Examiner and Sen teach that aneuploid tissues are cancerous or pre-cancerous. This argument has been fully considered but is not deemed persuasive. Applicants' statement is erroneous. Sen includes no teaching that all aneuploid tissues are cancerous or pre-cancerous, nor did the Examiner make any such statement. Rather, both Sen and the Examiner state that cancerous tissues are known to be aneuploid. It is also true that pre-cancerous tissues *may* be aneuploid. The converse is *not* true. Aneuploidy is also a feature of damaged tissue, and is commonly found in colon and lung tissues, which are subject to environmental damage. It does not invariably lead to cancer. Further, it remains that the 2-3 fold amplification of the nucleic acid is not predictive of a similar differential in protein expression; hence, the argument is not persuasive, as the claims are drawn to polypeptides, not the nucleic acids that encode them.

Applicants' argument of the Pennica reference at page 10 of the response has been fully considered but is not deemed persuasive. Applicants have plucked a single phrase from the portion cited by the Examiner, which phrase supports their assertion of utility. However, they have taken that phrase out of context; the teachings of Pennica as a whole support the opposite

conclusion, that utility of the polypeptide cannot be predicted based upon amplification of the nucleic acid, for reasons set forth at page 5 of the previous office action.

Applicants argument at pages 11-12 that there is expected to be a correlation between gene amplification and protein overexpression, with reference to an article by Orntoft et al., has been fully considered but is not deemed persuasive. Orntoft et al. *could only compare the levels of about 40 well-resolved and focused abundant proteins.*" (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Orntoft publication, and an associated rise in level of the encoded protein. The Hyman reference cited by applicants found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of SEQ ID NO: 222 would be correlated with elevated levels of mRNA. Further, Hyman does not examine protein expression. Applicants are reminded that the instant claims are directed to proteins. Similarly, Pollack, cited by applicants, does not analyze protein levels, nor does Pollack support the assertion that it is predictable, on the basis of the minimal increase in copy number of SEQ ID NO: 222 that the protein would accordingly be found at altered levels. Accordingly, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed protein. The art, taken as a whole, clearly teaches that it is not predictable that a two-fold copy increase in the nucleic acid would translate to detectable over-expression of the associated mRNA, much less any protein encoded thereby. Further, as evidenced by the Orntoft publication, the type of data presented in the instant specification clearly does not meet the standard in the art for establishing association of a protein with cancer.

At page 12, Applicant presents a discussion of the declaration by Dr. Polakis filed under 37 CFR 1.132 with the response. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer

diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1800 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 22-29, 35 and 37-41 based upon 35 U.S.C. §101 and §112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene *products* (such as the claimed polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Applicants argue ( page 18) that Hanna et al. teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 122-126 and 129-131 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record, and above.

Claims 122-124 and 130-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in the previous Office Action.

Applicants traversal that the recitation of a functional property in the claims overcomes the rejection. It is noted that the recitation "the nucleic acid encoding said polypeptide is amplified in lung tumors" is not a functional recitation *per se*, but rather a descriptor of where one might encounter the nucleic acids. This argument has been fully considered but is not deemed persuasive because applicants have not established that there is any conception of nucleic acids in a manner commensurate in scope with the claims, and hence of the claimed polypeptides. All applicants have presented is a single nucleic acid found to be slightly amplified in a small proportion of cancers, and the germ of an idea that there might be variants of the nucleic acid that would be similarly associated. There is no evidence of the actual conception of such nucleic acids, nor is there any evidence of record that they exist. Hence, there is accordingly no written description of the claimed polypeptides, other than the one identified as SEQ ID NO: 223. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Accordingly, the rejection is maintained.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person



having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 122-126 and 129-131 remain rejected under 35 U.S.C. 103(a) as being unpatentable over clone H74302, isolated by L. Hillier et al., WashUMerck EST Project 1995 in view of Sibson et al., WO94/01548 for reasons of record in the previous Office Action at page 9.

Applicants argument at page 16 of the response has been fully considered but is not deemed persuasive. The specification clearly states that the clone was purchased from Merck, and sequenced to obtain the sequence identified as PRO809. Applicants allegation to the contrary, in the absence of evidence, is not persuasive. In order to overcome this rejection, applicants must submit evidence in appropriate form as to what the actual sequence of the clone was, including an alignment to the claimed nucleic acids, in order for the Examiner to make a factual determination contrary to the admissions in the specification.

### ***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

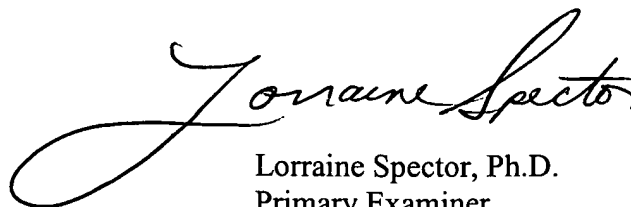
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to **571-273-0893**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.  
Primary Examiner

2/19/2005